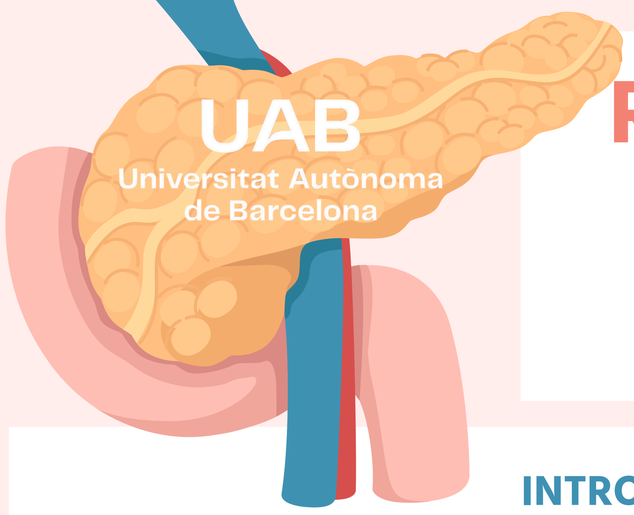


REPROGRAMMING PANCREATIC IDENTITY:

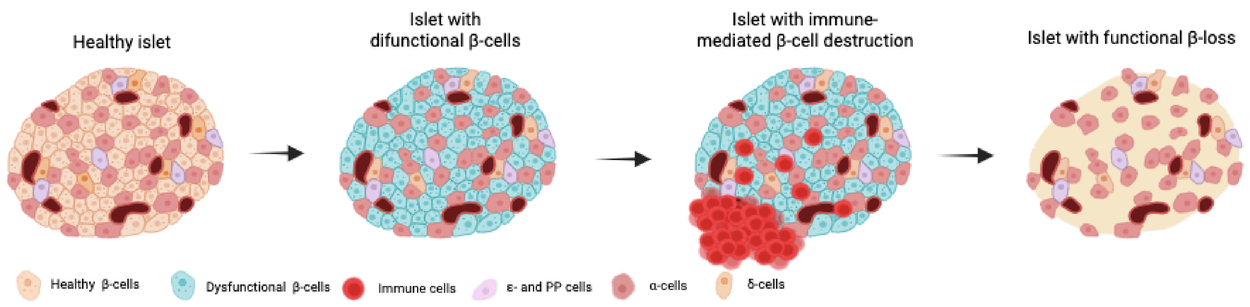
AAV-Based Gene Therapy for Alpha-to-Beta Cell Transdifferentiation in Type 1 Diabetes

Ariadna Serra Soria · 2024/2025 · Bachelor's thesis · Biotechonlogy Degree

INTRODUCTION

Type 1 Diabetes (T1D) is a chronic autoimmune disease characterized by the **destruction of pancreatic β-cells**, causing insulin deficiency. Current treatments rely on exogenous insulin, which poses challenges in accessibility and long-term management.

Alpha-to-beta cell transdifferentiation via AAV vectors offers a potential way to restore the body's ability to produce insulin and β-cells mass through the **intraductal delivery** of **Pdx1** and **MafA** transcription factors.



OBJECTIVES

1. **Contextualize Type 1 Diabetes Mellitus**, including pathophysiology and treatments.
2. **Characterize** alpha-to-beta cell transdifferentiation **gene therapy**.
3. Evaluate the **preclinical evidence** generated by **Genprex®**.
4. Examine **clinical translation challenges** of the gene therapy and **future perspectives.**

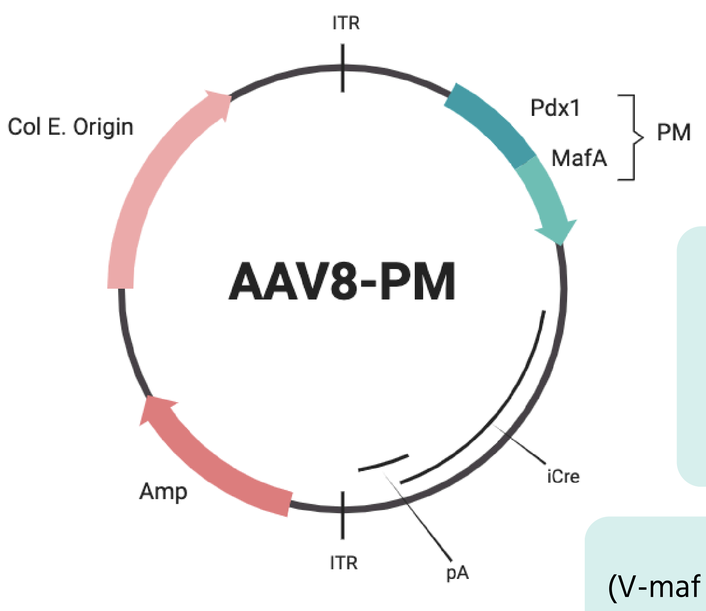
METHODOLOGY

ELSEVIER · Genprex · UNITED STATES PATENT AND TRADEMARK OFFICE · uspto

Search strategy based on keywords → Critical analysis and thesis development

AAV VECTORS AND CELLULAR PLASTICITY

Adeno-associated viral (AAV) vector

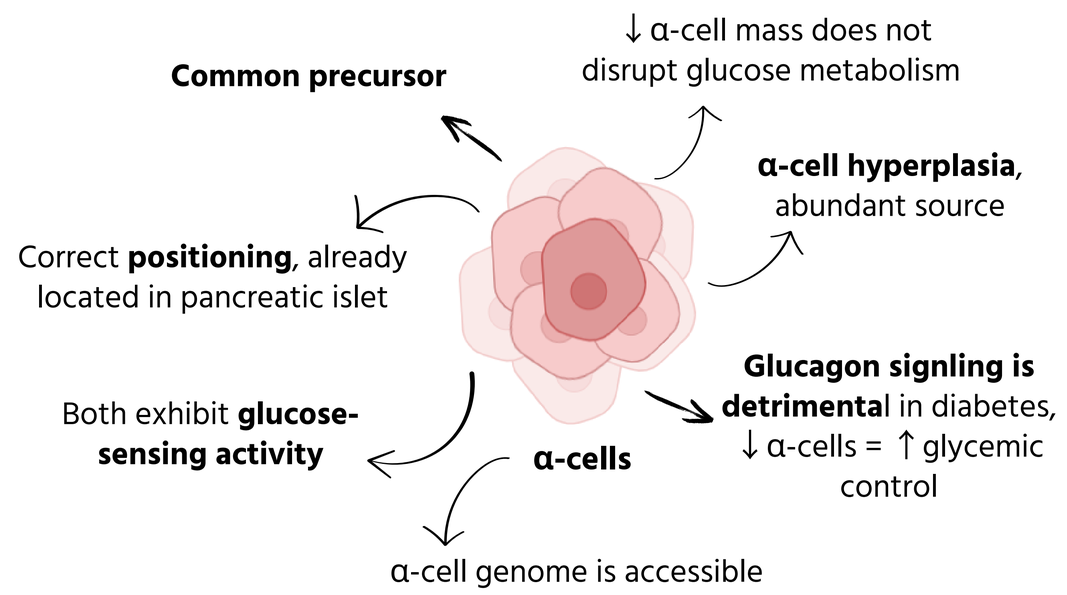


AAV Serotype 8:
- Long-term expression.
- Episomal.
- ↑ efficiency transducing α-cells.

Pdx1:
(Pancreatic duodenal homeobox)
- Formation of early pancreatic epithelium.
- Development, maturation and maintenance of β-cells.

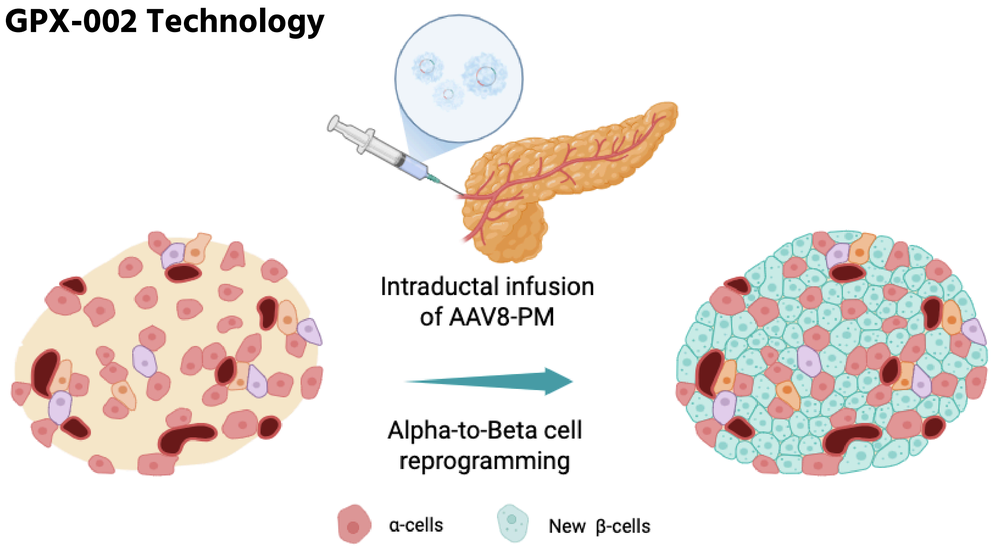
MafA:
(V-maf musculoaponeurotic fibrosarcoma oncogene homolog A)
- Maintenance of mature β-cells.

RATIONALE FOR α-CELLS



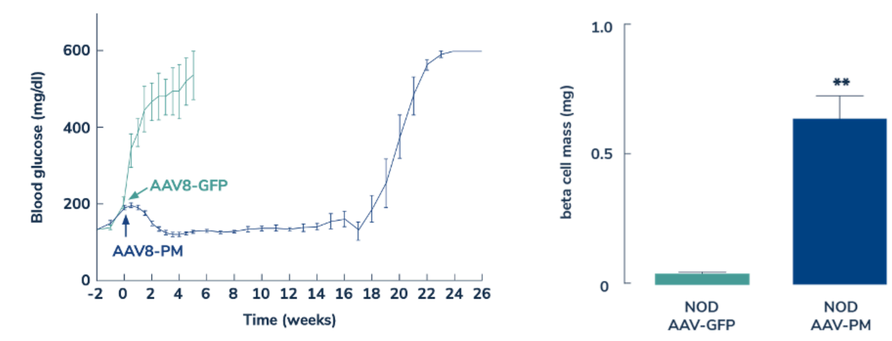
GENPREX®'S PRECLINICAL TRIALS

GPX-002 Technology

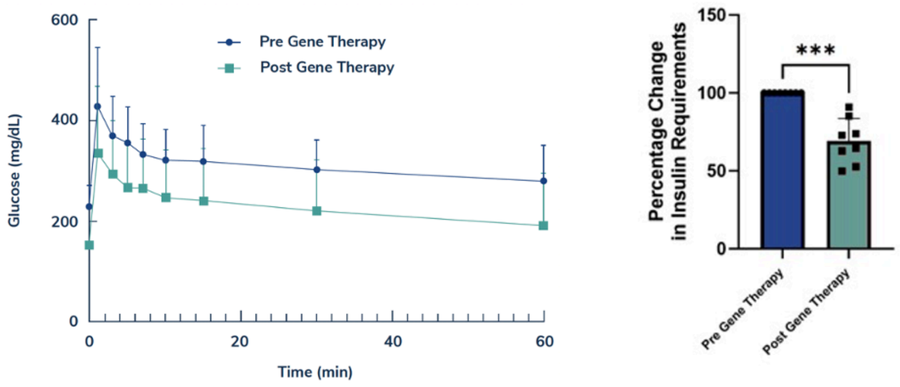


GPX-002:
- Transdifferenciates of α-cells to **achieve insulin production** and **secretion**.
- Infused through an **Endoscopic Retrograde Cholangiopancreatography (ERCP)**.

Results — University of Pittsburgh



GFP = Green Fluorescent Protein (fluorescent marker) | PM = Pdx1 + MafA



NOD mice:
(Non-Obese Diabetic)
- Sustained **normoglycemia** for 4 months.
- **In-transit cells**, α-cells expressing GCG and INS.
- Long-term expression.

NHPs:
(Non-Human Primates)
- Potential **applicability beyond rodent models**.
- Less insulin requirement.

Other results in Toxin-Induced Diabetic Mice and Human Islets:
- Decreased glycemia levels.
- Less susceptible to immune-mediated destruction.
- **Significant β-cell mass recovery**.
- Confirmation of reprogramming by lineage tracing.
- **Same AAV8 construct** for different models.
- **Increased endogenous insulin** production, C-peptide levels, and **glucose tolerance**.

CONCLUSIONS

- **Recovery of pancreatic function**.
- **Translational potential**, although evaluation of the therapy's safety, immunogenicity and dosage are required.
- Personalization of the treatment according to patients immunological responses.
- **Limited durability** of the treatment.
- Potential need for combination with **immunosuppressants**.
- High cost represents a socioeconomic barrier.
- Off-target **long-term effects of Pdx1** and **MafA**.
- Pre-infection with AAV excludes some patients.
- Does **not address** the **immune attack**.
- Could transform **T1D** into a **more manageable** disease with a lesser impact on patient's quality of life.

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